Development and biopharmaceutical evaluation of osmotic pump tablets for controlled delivery of diclofenac sodium

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Received April 23, 2003
Accepted November 17, 2003

Based on the principles of an elementary osmotic pump (OP), OP tablets were designed and evaluated with the aim to deliver diclofenac sodium (DS) in a controlled manner. In vitro evaluation was done in various release media and kinetics was evaluated using the regression coefficient analysis. Effects of orifice size, coating membrane type, coating thickness, static and stirred conditions and pH variation were studied. In vivo evaluation was performed on six healthy human volunteers and various pharmacokinetic parameters ($c_{\text{max}}$, $t_{\text{max}}$, $AUC_{0-24}$, MRT) and relative bioavailability were calculated. The results were compared with the performance of two commercial tablets of DS. The drug release from OP tablets was dependent on the type and thickness of the coating membrane, but was independent of the orifice size and static and stirred conditions of the release medium. The OP tablets provided a prolonged and controlled DS release compared to commercial sustained-release and conventional tablets of DS.

Keywords: osmotic pump, diclofenac sodium, controlled release, bioavailability, pharmacokinetics

Studies of the controlled release of drugs for their extended and safe use have recently become an important field of research (1). Among controlled-release devices, osmotically driven systems hold a prominent place because of their reliability and ability to deliver the contents at predetermined zero-order rates for prolonged periods (2–7). Osmotic pumps (OP) are standard dosage forms for a constant-rate drug delivery (8–10). Preparation of an elementary osmotic pump consists of the core containing the active material and a semipermeable membrane that coats the core, having a microdrill produced orifice in order to release the active material. When the system happens to be inside the gastrointestinal tract, the fluid enters the core through the membrane and dis-

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solves the active material. The osmotic pressure generated in the core induces release of the drug in solution at a slow but constant rate (11, 12). To gain the advantages of pH and agitation independent release performance leading to similar in vitro/in vivo delivery, osmotically active drug delivery systems have been extensively investigated (12–15).

Diclofenac sodium (DS) is a potent non-steroidal anti-inflammatory agent. It has a relatively short biological half-life and suffers from the hazards of adverse gastro-intestinal reactions. Therefore, the development of oral sustained/controlled release formulations of this drug is highly desirable. Many efforts have been made towards achieving sustained release formulations of DS (16–25). Hence, the present work was aimed to design, develop and evaluate an oral osmotic delivery system of DS, directed towards achieving a better therapeutic effect and bioavailability of this drug.

EXPERIMENTAL

Materials

Diclofenac sodium was obtained as a gift sample from Win-Medicare Ltd., India. Commercial tablets of DS [batches C10 (Voveran-SR) and C11 (Voveran- 2x50 mg conventional tablet)], each containing 100 mg drug, were the products of Novartis India Ltd. (India). Cellulose acetate (CA), polyethylene glycol (PEG 400) and microcrystalline cellulose were obtained from Thomas Baker (Chemicals) Ltd., Glaxo Lab Ltd. and S.D. fine Chem. Ltd., all from India. All other chemicals/reagents used were of analytical grade, except for those used in HPLC analysis, which were of HPLC grade.

Preparation of osmotic pump tablets of DS

Preparation of core tablets. – Accurately weighed quantities of ingredients mentioned in Table I were passed through sieve No. 85 (aperture size 180 μm, British Standard). All the ingredients, except lubricant (magnesium stearate), glidant talc and binder polyvinylpyrrolidone (PVP), were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution of 10% (m/V) PVP, and granulated through sieve No. 18 (aperture size 1000 μm, US Standard) and dried in a hot air oven at 60 ºC for sufficient time (3 to 4 hours) so that the moisture content of the granules reached 2–4%. The dried granules were passed through sieve No. 26 (aperture size 710 μm, US Standard) and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets (300 mg each) using 10-mm diameter, deep concave punches. The compression force was adjusted to give tablets with approximately 7 kg cm⁻² hardness on a Monsanto tablet hardness tester (Campbell Electronics, India).

Coating of core tablets. – Core tablets were film coated with either a semipermeable membrane of 2% (m/V) cellulose acetate (CA) in acetone with castor oil (20%, m/m, total solid CA) as plasticizer or with a microporous membrane consisting of PEG 400 (20%, m/m, total solid CA) incorporated in CA using a conventional laboratory model, stainless steel, 10-cm pear shaped, baffled coating pan. The manual coating procedure used
was based on an intermittent spraying and drying technique and an orifice through the membrane was made by a microdrill on one side of the tablet (26).

In vitro studies

In vitro studies were done using a USP 24 (27) dissolution apparatus II in different release media (pH 7.4, pH 6.8, distilled water) maintained at 37 ± 0.2 °C and 100 rpm. Withdrawn samples were analyzed on a Jasco UV/VIS spectrophotometer (model 7800, Jasco, Japan) at 275 nm. The experiments were performed in triplicate. To study the effect of agitation intensity, in vitro studies were performed at 50 rpm, 100 rpm and under static conditions. Under static conditions, samples were taken at different times after uniform mixing of the medium (10).

In vivo studies

In vivo studies were performed following the standard protocols in six healthy human volunteers of either sex weighing 55–75 kg and 24–29 years old in a cross-over design. Volunteers agreed in writing to participate in the study after being informed about the experimental protocol. All subjects were in good health according their medical history and complete physical examination. The volunteers neither smoked nor were on

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Table I. Composition and physical parameters of fabricated osmotic pump tablets

<table>
<thead>
<tr>
<th>Ingredient (mg per OP tablet)</th>
<th>OPIa</th>
<th>OPIb</th>
<th>OPIc</th>
<th>OPId</th>
<th>OPIIa</th>
<th>OPIIb</th>
<th>OPIIc</th>
<th>OPIId</th>
<th>OPIIIa</th>
<th>OPIIVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>MCC</td>
<td>182</td>
<td>182</td>
<td>182</td>
<td>182</td>
<td>142</td>
<td>142</td>
<td>142</td>
<td>142</td>
<td>122</td>
<td>117</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Potassium bicarbonate</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>25</td>
</tr>
<tr>
<td>SLS</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
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<tr>
<td>Talc</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nature of coating</td>
<td>SP</td>
<td>SP</td>
<td>SP</td>
<td>MP</td>
<td>SP</td>
<td>SP</td>
<td>SP</td>
<td>SP</td>
<td>SP</td>
<td>SP</td>
</tr>
<tr>
<td>Coat thickness (µm)</td>
<td>40.1 ± 40.2 ± 40.0 ± 80.2 ± 100.2 ± 40.1 ± 79.9</td>
<td>40.2 ± 40.0 ± 40.0 ± 80.2 ± 100.2 ± 40.1 ± 79.9</td>
<td>40.0 ± 40.0 ± 40.0 ± 80.2 ± 100.2 ± 40.1 ± 79.9</td>
<td>40.2 ± 40.2 ± 40.2 ± 40.2 ± 40.2 ± 40.2 ± 79.9</td>
<td>40.1 ± 40.2 ± 40.0 ± 80.2 ± 100.2 ± 40.1 ± 79.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orifice diameter (µm)</td>
<td>–</td>
<td>500</td>
<td>500</td>
<td>–</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>–</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

1 OP – osmotic pump tablet; 2 DS – diclofenac sodium; 3 MCC – microcrystalline cellulose; 4 SLS – sodium lauryl sulphate; 5 SP – semi-permeable; 6 MP – microporous
any kind of medication before or during the experiment. The experiment protocol was approved by the Ethical Committee, BHU, India.

The modified HPLC method (28) was used to analyze human plasma samples, (stored at −20 °C until analysis) at different time intervals up to 24 hours following oral administration of formulated OP tablets as well as two commercial tablets (C10 and C11) to human subjects. Isocratic HPLC procedure was carried out using Novapak C-18, 4 μm (150×3.9 mm), column (Shimadzu, Japan) and acetonitrile 0.025 mol L⁻¹ ammonium acetate (40:60) as a mobile phase at a flow rate of 1 mL min⁻¹. Injected volume was 75 μL and detection was performed at 275 nm using a UV detector (Shimadzu).

Statistical analysis

Experimental results were expressed as mean ± SD values. Student’s t test was performed to determine the level of significance. Differences were considered to be statistically significant at \( p < 0.05 \).

RESULTS AND DISCUSSION

The core of OP tablets contained the drug, microcrystalline cellulose (MCC) as diluent, potassium chloride and potassium bicarbonate as osmogents, sodium lauryl sulphate (SLS), a surfactant for proper core wetting with imbibition medium, talc as glidant and magnesium stearate as lubricant. The various physical parameters evaluated for all fabricated OP tablets were found to be within official limits. It was observed from release profiles (Fig. 1) that an increase in membrane thickness affected the drug release rate inversely. All three tablets (OPIIa, OPIIb, OPIIc) exhibited constant and controlled drug release profiles from one hour onwards, though showing slow drug release till the first hour, which must have elapsed in inhibition of the core with the release medium. The drug release from the osmotic pump tablets batches OPld and OPlld (coated with a
membrane that becomes microporous due to dissolution of PEG 400 by the medium), followed the Higuchi kinetics and diffusion mechanism of drug release as compared to OPIb and OPIa batches (coated with a semipermeable membrane) that exhibited zero-order kinetics of drug release (Table II). OPId and OPIId batches gave higher and non-linear drug release profiles (Fig. 2) due to the fact that when they came in contact with the aqueous environment during the release study, the water soluble PEG 400 leached out leaving behind the microporous membrane on the surface of the core tablet, which allowed free diffusion of drug molecules along the concentration gradient. Membranes in OPIb and OPIa batches behaved like true semi-permeable membranes, resulting in zero-order delivery of drug through the orifice only under the control of osmotic pressure gradient across the membrane, as evidenced by the kinetic data shown in Table II.

Table II. Kinetics of in vitro DS release from different batches of osmotic pump tablets

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPIa</td>
<td>0.9998</td>
<td>0.8900</td>
<td>0.9948</td>
</tr>
<tr>
<td>OPIb</td>
<td>0.9954</td>
<td>0.9134</td>
<td>0.9308</td>
</tr>
<tr>
<td>OPIc</td>
<td>0.9953</td>
<td>0.8935</td>
<td>0.9314</td>
</tr>
<tr>
<td>OPId</td>
<td>0.9864</td>
<td>0.9297</td>
<td>0.9980</td>
</tr>
<tr>
<td>OPIIa</td>
<td>0.9999</td>
<td>0.9154</td>
<td>0.9895</td>
</tr>
<tr>
<td>OPIIb</td>
<td>0.9999</td>
<td>0.9410</td>
<td>0.9894</td>
</tr>
<tr>
<td>OPIIc</td>
<td>0.9997</td>
<td>0.9473</td>
<td>0.9876</td>
</tr>
<tr>
<td>OPIId</td>
<td>0.9860</td>
<td>0.9270</td>
<td>0.9978</td>
</tr>
<tr>
<td>OPIIIa</td>
<td>0.9999</td>
<td>0.8855</td>
<td>0.9911</td>
</tr>
<tr>
<td>OPIIVb</td>
<td>0.9999</td>
<td>0.9375</td>
<td>0.9902</td>
</tr>
</tbody>
</table>

* Analyzed by the regression coefficient method.

Fig. 2. In vitro release profiles showing the effect of semipermeable (batches OPIb and OPIa) and microporous coating (batches OPId and OPIId) on DS release from OP tablets in pH 7.4 buffer. Bars represent SD values (n = 3).
Though the DS release decreased with an increase in coating thickness (Fig. 1), variation in orifice size (500 and 1000 \( \mu m \)) showed no significant effect on the rate and extent of DS release from OP tablets (Fig. 3). Since no burst effect was observed during the drug release study, it can be inferred that the two selected orifice sizes (500 and 1000 \( \mu m \)) had successfully prevented the membrane from rupturing by effectively releasing the hydrostatic pressure developed inside the system and at the same time delivered the drug at a constant rate over a sufficiently long period of time (12, 29). In order to simulate complete blocking of the delivery orifice, the release of DS from coated OP tablets without an orifice (OPIa) was studied (Fig. 3). Profiles exhibited prolonged drug release but with linearity maintained after 2 hours of lag period. This is in agreement with our earlier studies on osmotic pump tablets of naproxen sodium (10), wherein we reported that continuous water influx into the system produced an increase in the volume of the
drug solution inside the coated tablet (without orifice) and this led to an increase of the hydrostatic and osmotic pressure inside the tablet. The pressure thus generated caused expansion and/or weakening of the membrane, which in turn led to the formation of pore(s) in the membrane or increased the size of the existing micropores, thereby delivering the contents via an osmotic delivery mechanism. This clearly indicates that even in the case of accidental blockage of the orifice of OP tablets, it is likely that there will be neither dose dumping nor failure of drug delivery and drug release may still follow a zero-order release pattern.

It was observed (Fig. 4) that the osmotic pump tablets OPIIIa and OPIVb having the same orifice diameter (500 μm) but different coat thickness (40 and 80 μm, respectively) studied under stirred and static conditions exhibited no significant difference in the rate and extent of DS release. However, OPIVb tablets having coating membranes twice as

Fig. 5. In vitro release profiles showing the effect of pH variation on DS release from OP tablets. Bars represent SD values (n = 3).
thick as OPIIIa exhibited a significantly reduced rate and extent of drug release compared to the latter. Drug release from OP tablets performed in phosphate buffers of pH 7.4 and pH 6.8, and in water also resulted in a non-significant difference in DS release from OP tablets (Fig. 5) (30, 31). The in vitro drug release kinetics of OP tablets was studied by the regression coefficient analysis (32), as shown in Table II. All OP tablets, except for OPIId and OPIMId tablets, showed zero-order kinetics of drug release. OPIId and OPIMId tablets with microporous coatings followed the Higuchi diffusion kinetics.

The plasma DS concentration vs. time profiles (Fig. 6) obtained from in vivo studies clearly show that OP tablets maintained a constant therapeutic DS concentration (33) within plasma even up to 24 hours, as compared to commercial formulations C10 and C11 which showed a higher rate of drug concentration decrease as a function of time. The fabricated OP tablets studied in vivo showed lower $c_{\text{max}}$ (but within therapeutic range) (33) and higher $t_{\text{max}}$ values than commercial tablets (C10 and C11) (Fig. 6). Lower $c_{\text{max}}$ for OP tablets indicates the avoidance of intense pinching, thus avoiding the risk of exceeding the maximum safe concentration. Higher $t_{\text{max}}$ for OP tablets is indicative of drug release occurring at a slower rate than from commercial tablets. Significantly high-

<table>
<thead>
<tr>
<th>Batch code</th>
<th>$c_{\text{max}}$ (µg mL$^{-1}$)$^a$</th>
<th>$t_{\text{max}}$ (h)$^a$</th>
<th>AUC$_{0-24}$ (µg mL$^{-1}$)$^a$</th>
<th>RB$_1$ (%)$^a$</th>
<th>RB$_2$ (%)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPIIIa</td>
<td>0.331 ± 0.060</td>
<td>6.0 ± 0.2</td>
<td>4.98 ± 0.12</td>
<td>108</td>
<td>138</td>
<td>13.3</td>
</tr>
<tr>
<td>OPIVb</td>
<td>0.310 ± 0.061</td>
<td>6.0 ± 0.3</td>
<td>5.35 ± 0.22</td>
<td>116</td>
<td>148</td>
<td>14.8</td>
</tr>
<tr>
<td>C10</td>
<td>0.501 ± 0.054</td>
<td>4.0 ± 0.5</td>
<td>4.61 ± 0.28</td>
<td>100</td>
<td>128</td>
<td>8.6</td>
</tr>
<tr>
<td>C11</td>
<td>0.781 ± 0.081</td>
<td>2.0 ± 0.5</td>
<td>3.60 ± 0.28</td>
<td>78</td>
<td>100</td>
<td>3.7</td>
</tr>
</tbody>
</table>

$^a$ Mean ± SD (n = 6)

AUC – area under the curve
RB – relative bioavailability
RB$_1$ – with reference to C10 (SR Voveran – SR)
RB$_2$ – with reference to C11 (conventional Voveran)

Fig. 7. Correlation between the in vitro percent DS release and plasma DS concentrations for fabricated osmotic pump tablets (OPIIIa and OP IVb) at 2, 4 and 6 hours.
er values of $AUC_{0-24}$, relative bioavailability and mean residence time (MRT) for OP tablets in comparison to C10 and C11 (Table III) further indicate the superiority of fabricated OP tablets over commercial SR (C10) and conventional (C11) tablets of DS, in terms of providing controlled drug release for longer time and improved bioavailability. Further, in vitro data and plasma DS concentration after 2, 4 and 6 hours for OPIIIa and OPIVb (Fig. 7) exhibited a good correlation (34, 35).

CONCLUSIONS

This study suggests that the OP tablets of DS could perform therapeutically much better than the commercial conventional DS tablets, as potential prolonged and controlled release dosage forms, which may lead to improved efficacy and better patient compliance.

Acknowledgement. – We thank Mr. Vinod Arora and Mr. Tausif (Ranbaxy Laboratories Ltd., Gurgaon, India) for providing HPLC facilities for carrying out in vivo studies.

REFERENCES

Razvoj i biofarmaceutsko vrednovanje tableta diklofenak-natrija
na principu osmotske pumpe

MEENA RANI, RAHUL SURANA, CHELLADURAI SANKAR i BRAHMESHWAR MISHRA

Na principu osmotske pumpe (OP) pripravljene su i evaluirane OP tablete diklofenak-natrija. In vitro evaluacija provedena je u različitim medijima. Proučavan je utjecaj veličine pora, vrste i debljine ovojnice, te utjecaj miješanja i pH na kinetiku oslobađanja. In vitro evaluacija provedena je na đest zdravih dobrovoljaca. Određeni su različiti farmakokinetički parametri ($c_{\text{max}}$, $t_{\text{max}}$, $AUC_{0-24}$, MRT) i relativna bioraspoloživost. Rezultati su uspoređivani s dvije vrste registriranih tableta diklofenak-natrija. Oslobađanje ljekovite tvari iz OP tableta ovisilo je o vrsti i debljini ovojnice, a nije ovisilo o veličini pora i uvjetima miješanja u mediju za oslobađanje. U odnosu na komercijalne tablete sa i bez produljenog oslobađanja DS-a, OP tabletama postignuto je produljeno i kontrolirano oslobađanje ljekovite tvari.

Ključne riječi: osmotska pumpa, diklofenak-natrij, kontrolirano oslobađanje, bioraspoloživost, farmakokinetika

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